Statistical Analysis Plan

A Trial of Favipiravir and Hydroxychloroquine combination in Adults Hospitalized with moderate and severe Covid-19

Study Code : RC20/174/R

Study Protocol Version/ Date : Version: 3.1 (11AUG 2020)

Organization : KAIMRC

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Signature Page

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Name	Role& Organization	Signature	Approval Date
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LIST OF ABBREVIATIONS

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ADR	Adverse Drug Reaction
AE	Adverse Event
AFP	Alpha- fetoprotein
CRF	Case Report Form
eCRF	Electronic Case Report Form
ICH	International conference on harmonization
ITT	Intention to treat
ICH	International conference on harmonization
KAIMRC Research Center	King Abdullah International Medical
KAMC	King Abdul-Aziz Medical City

1. INTRODUCTION

In general, the Statistical Analysis Plan (SAP) purpose is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials (1). All work planned and reported for this SAP will follow national and international guidelinesfor statistical practice (2-5).

The planned analyses identified in this SAP will be included in future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be clearly identified as such in manuscripts for publication.

The following documents were reviewed when preparing this SAP:

- Clinical Research Protocol
- Final approved codebook
- ICH Guidance on Statistical Principles for Clinical Trials(1).
- ICH Guidance on Structure and Content of Clinical Study Reports(6).

The reader of this SAP is encouraged to read the clinical study protocol for details on this study's conduct and the operational aspects of clinical assessments and timing for completing a patient in this study.

All data analyses and generation of results will be performed using SAS 9.4.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The improvement of two points (from the status at randomization) on a seven-category ordinal scale* or live discharge from the hospital, whichever came first.

*The seven-category ordinal scale consists of the following categories:

1. Not hospitalized with resumption of normal activities

2. Not hospitalized, but unable to resume normal activities

3. Hospitalization, not requiring supplemental oxygen

4. Hospitalization, requiring supplemental oxygen

5. Hospitalization, requiring nasal high-flow oxygen therapy and/or non-invasive mechanical ventilation

6. Hospitalization, requiring ECMO and/or invasive mechanical ventilation

7. Death.

2.2. SECONDARY OBJECTIVE

1. To evaluate the progress in the clinical status of COVID-19 patients in both arms

2. To monitor the viral shedding duration and PCR test conversion days from positive to negative.

3. Evaluate the safety of investigational therapeutics as compared to the control arm.

4. To evaluate the difference in the complications and prognosis of COVID-19 patients between the two groups.

3. STUDY DESCRIPTION

3.1. STUDY DESIGN

This study is a randomized, controlled, open-label trial to evaluate novel therapeutic agents' safety and efficacy in hospitalized adults diagnosed with COVID-19. It is a multicenter trial that will compare Favipiravir plus Hydroxychloroquine combination (experimental arm) to a control arm.

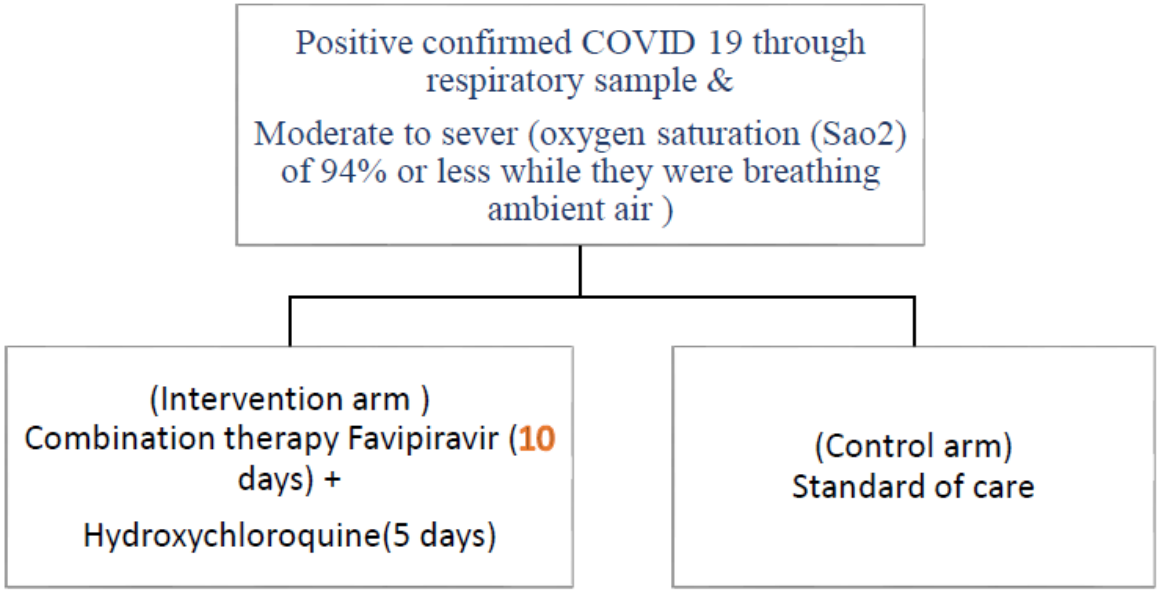


Figure 1: Study Design

3.2. RANDOMIZATION PROCEDURE

This study will employ a manual randomization scheme using a computer-generated random allocation schedule. Patients who meet the enrollment criteria and have provided written informed consent will be randomized to one of two treatment groups: (1) Favipiravir and Hydroxychloroquine or (2) control group.

The randomization number (RN) is a unique number and once assigned, it will become the permanent identifier for that patient. In the event a patient is enrolled in the study but does not begin or continue treatment, that patient's randomization number will not be reassigned. Patients who do not meet entry criteria will not be assigned an allocation number.

A single patient/subject cannot be assigned more than 1 randomization number.

3.3. STUDY DURATION

The treatment intervention would be for a maximum of 10 days from randomization, and it would be as follow:

Favipiravir for 10 days as follow:

Administer 1800 mg (9 tablets) by mouth twice daily for one day, followed by 800mg (4 tablets) twice daily (total days of therapy is 10 days)

Hydroxychloroquine for 5 days:

(400mg) twice daily on day 1; for days 2-5 (200mg) twice daily.

3.4. SCHEDULE OF ASSESSMENTS

A summary of the scheduled study evaluation is presented in the table overleaf.

	Study period											
	Baseline	Post allocation										Closeout
Timepoint study days	D0	D1	D2	D''	D5	D''	D9	D10	D''	D14	D21	D28
Enrolment and assignment												
Eligibility assessment	X	X										
Informed consent	X	X										
Randomization	X	X										
Baseline data	X	X										
Study drug administration												
Favipiravir		X	X	X	X	X	X	X				
Hydroxychloroquine		X	X	X	X							
Adverse effect reaction		X	X	X	X	X	X	X	X	X		
Serious adverse event assessment		X	X	X	X	X	X	X	X	X	X	X
Clinical data collection												
Seven-category ordinal scale and CRF	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory data collection												
Covid-19 PCR from Respiratory sample *	X	X			X			X		X	X	X
CBC, renal profile and LFT on Study Drug	X	X	X	X	X	X	X	X		X	X	
CBC, renal profile and LFT on SoC	X	X			X			X			X	
ECG for patient on Study Drug	X	X	X	X	X			X				
ECG for patient on SoC	X	X			X			X				

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

The primary endpoint is the time to clinical improvement, defined as the time from randomization to an improvement of at least two points (from the status at randomization) on a seven-category ordinal scale or live discharge (2) from the hospital, whichever came first.

4.2. Secondary Endpoint(s)

1. Clinical status assessed by the seven-category ordinal scale.
2. The requirement of ICU admission or Mechanical ventilation
3. 28- and 90-days mortality.
4. PCR test negative conversion rate and days from positive to negative**
5. Evaluate the safety of investigational therapeutics as compared to the control arm.
6. Length of hospital stay.
7. Duration of fever.
8. QT prolongation (Daily follow up during the concomitant use of both medications and regularly till Day 14)

4.3. Safety Outcome Measures:

Safety assessments will monitor and record all adverse events and serious adverse events occurring during the regular monitoring of hematology and blood chemistry, ECG, regular measurement of vital signs, and performance of physical and neurological examinations if needed.

4.4. Other exploratory endpoints (S)

Not applicable

5. SAMPLE SIZE AND POWER

5.1. ASSUMPTIONS AND STUDY HYPOTHESIS:

1. Time to discharge or clinical improvement by 2 points in the standard of care arm is expected to be (median: 11 days; Cai Q, Y.M., Liu D, Chen J, Shu D, Xia J, , Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. 2020.).
2. The exact treatment effect from Favipiravir tables + Hydroxchloroquine is not exactly known but can be approximated using prior clinical studies. A study comparing the effect of Favipiravir to lopinavir/ritonavir on virus clearance has shown a 64% reduction in time to viral clearance in the Favipiravir arm. This was equivalent to a median of 11 days. We assume that clinical improvement might take place a little later to viral clearance and therefore, we assume that the treatment arm might result in a minimum clinically meaningful expected reduction of 30% (Median 7.7 days). This is equivalent to a Hazard ratio of 0.7.
3. We further assume that 50% of the patients in the control group will have clinical improvement/ discharged and 70% will have clinical improvement/discharged in the treatment arm
4. It is anticipated that very few of these subjects will be randomized and not start study treatment (and so be excluded from the primary analysis) or be lost to follow-up (and so have missing data for the primary endpoint). Given certain uncertainties, however, we have included a nominal 10% drop-out rate.

5. The primary hypothesis of the current study is H0: HR =1 vs. H1: HR □1 ; and HR is the hazard ratio of treatment compared to control arm.

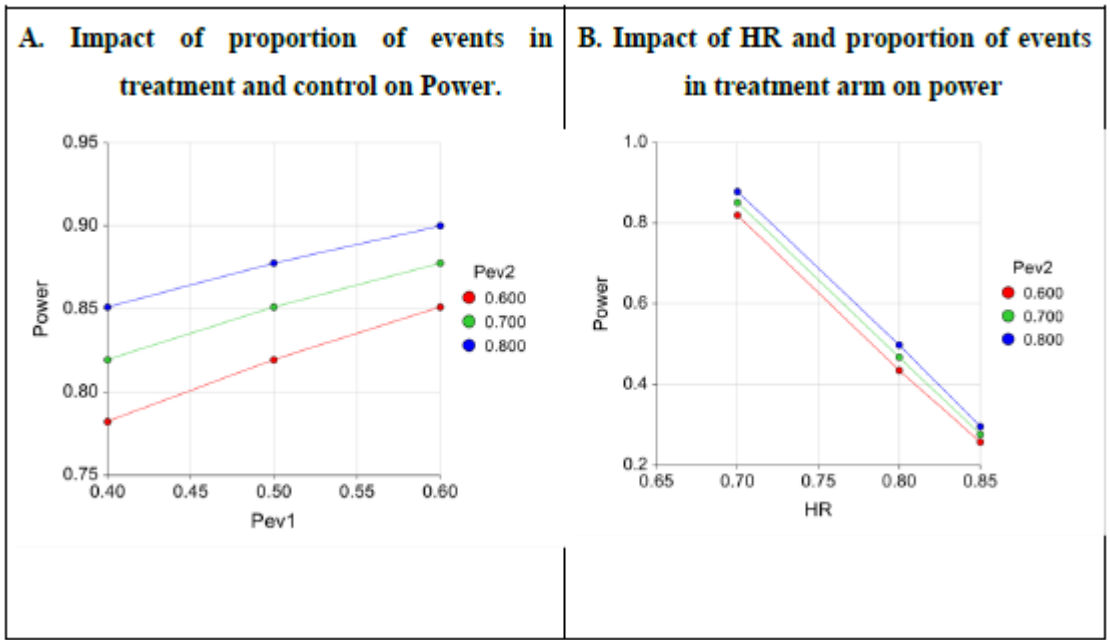
5.2. SAMPLE SIZE ESTIMATION FOR CLASSICAL TWO ARM PARALLEL DESIGN:

Under the classical two arms parallel design, the total effective sample sizes needed is 472 subjects (236 subjects per group). The Estimated sample size achieves 85 % power to detect a minimum of 30% reduction in the median time, to clinical improvement by at least two points or hospital discharge in the treatment group compared to the control group. The treatment arm's median time is 11 days under the null hypothesis and 7.7 days under the alternative hypothesis. The median time in the control group under the null hypothesis is 11 days. The two survival curves will be analyzed using a one-sided Cox proportional hazard regression. The significance level of the test is 0.025. Assuming a 10% drop out rate, the trial's overall sample size is estimated to be 520 (260 per group). Sample size adjustment will be considered after an interim analysis of 60% of the subjects' recruitment and based on DSMB recommendation. DSMB chair and members voted for an early interim analysis at 268 subjects (51.5%) due to logistic issues.

5.3. SENSITIVITY ANALYSIS

We have performed several sensitivity analyses to determine the effect of different assumptions on the sample size. Figure 2A shows the relationship between the proportion of event in the treatment (Prev2), the proportion of events in control (Prev1), and the study's power. An increase in both groups' events leads to increased overall study power up to 90%. A simultaneous decrease in the events could lead to less power to as low as 78%. Reduction of events in the treatment group alone does not lead to loss of power below the accepted norm of 80%. Because the reduction in the proportion of events in the treatment group has the largest impact, we examined the impact of overestimating the HR and the proportion of events in the treatment group on power. Figure 2B shows that regardless of the number of

events, a slight change in the HR than the assumed will severely impact power. However, the current design could accommodate an overestimation of HR by only 10% (.27 instead .3) before power falls under desired level.



6. STUDY POPULATIONS

6.1. INTENTION-TO-TREAT POPULATION (ITT)

The Intent-to-Treat (ITT) population will include all patients randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different. The ITT population will be used for all efficacy analyses of efficacy endpoints unless specified otherwise.

6.2. PER-PROTOCOL POPULATION **(PP)**

The Per-Protocol (PP) population will include all randomized patients who do not have a major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made before database lock.

The PP population will be used as a supplement to the ITT population's analysis for the primary efficacy endpoint.

All patients in the PP population will be analyzed according to the actual treatment received.

6.3. SAFETY POPULATION

The safety population will include all enrolled patients who have received at least 1 dose of study medication. All patients in the safety population will be analyzed according to the actual treatment received.

All safety analyses will be performed using the safety population.

ENDPOINTS/ ANALYSIS	POPULATION /ANALYSIS SETS
Subject Disposition	ITT Population
Demographic and Baseline Characteristics	ITT Population
Efficacy Analysis	ITT Population, PP population
Safety Analysis	ITT Population, Safety Population
All Listings (If any)	ITT Population

7. HYPOTHESES AND DECISION RULES

7.1. STATISTICAL HYPOTHESES

The primary hypothesis to be tested:

The primary null hypothesis is that there is no difference in clinical improvement between two groups. The alternative hypothesis is that the Combination therapy of Favipiravir and Hydroxychloroquine will improve clinical improvement.

7.2. TESTING SIGNIFICANCE FOR PRIMARY ENDPOINT

Time to clinical improvement will be tested at a 1-sided significance level of 0.025. We will conclude that combination therapy can reduce the median time to clinical improvement by at least two points or hospital discharge compared to the control group.

7.1. HANDLING DROPOUTS AND MISSING DATA

All missing data will be reviewed and characterized in terms of their pattern (eg. Missing completely at random, missing at random, etc.). All analyses will be based on a list-wise deletion approach where observation will complete values will be only considered for analysis for missing completely at random. For variables with values missing at random, multiple imputation techniques will be utilized to impute the missing values as suggested by Rubin's (1987).

7.2. ADJUSTMENT FOR MULTIPLICITY

To adjust for multiple testing, we will use the False Discovery Rate (FDR) as described by Benjamini and Hochberg [13]. In this procedure all hypothesis tests will be sorted in an

ascending order based on their calculated p-value. All hypothesis tests below an index K will be rejected where K calculated as follows:

$$K = max\left\{i : p(i) \leq \frac{i}{m}.q\right\}$$

Where i=m, …1 ; m is the number total number of tested hypotheses ; q =.05.

7.3. STATISTICAL SOFTWARE

All analyses, including the interim and final analysis, will be analyzed using SAS version 9.4 NC.

8. DATA SAFETY MONITORING COMMITTEE (DSMB)

An DSMB will review safety and efficacy data at the interim analysis. The DSMB will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on the DSMB recommendation, KAIMRC will notify the appropriate regulatory authorities. Detailed information regarding the composition of the DSMB and detailed DSMB procedures will be provided in the DSMB charter.

The first formal safety review will occur after the recruitment and follow-up of 60% of the total number of subjects (i.e. 312).

There will be one interim analysis in this study.

The current study will have a single interim analysis, which will take place after the recruitment and follow-up of 51%of the total number of subjects (i.e. 264) included the drop-outs. The interim analysis is designed to test for early stopping for futility or efficacy and sample size re-estimation. The interim analysis and final analysis will be based on the method of the sum of the stage-wise p-value discussed in Mark and Chang, 2008. The table below describes the interim analysis testing boundaries.

Boundary	Decision
Alpha1 = 0.01	Stop the trial for early efficacy if the interim analysis p-value is less than 0.01
Beta1 =0.25	Stop the trial for futility if the interim analysis P-value is equal to or larger than 0.25
Alpha2=0.1832	Declare the trial significant if the sum of the interim analysis and final stage P-values are less than 0.1832

9. DESCRIPTION OF TABLES AND FIGURES

9.1. SUBJECT DISPOSITION

The number and percentage of randomized patients in each group will be reported. We will report the number of randomized patients who received the interventions. We will also report the number of screened patients (defined as all hospitalized patients with COVID-19), who met the eligibility criteria but not enrolled and reasons for non-enrollment. A CONSORT flow diagram of the trial progress will be constructed.

9.2. PROTOCOL VIOLATIONS/ DEVIATIONS

Potential violations that may result in the exclusion of a patient from the Per-Protocol population include:

- Patient compliance with study medication is <80%,
- Premature discontinuation of treatment

9.3. BASELINE AND DEMOGRAPHIC CHARACTERISTICS

9.3.1. Demographic and baseline Characteristics

We will summarize and report the demographics and baseline clinical characteristics using descriptive statistics. Baseline characteristics will be presented for the two study groups, including age, sex, and body mass index, and co-infections. We will report co-morbidities and the interventions received before randomization for patients in each group. We will report baseline laboratory values (international normalization ratio, platelet count, hemoglobin, white blood cell count, lymphocyte count, glucose, neutrophil count, uric_acid, total bilirubin, AST/SGOT, ALT/SGPT, Blood Urea Nitrogen (BUN), Lactate/Lactic acid, Creatinine, Sodium, Potassium, Procalcitonin, CRP), respiratory and vital parameters in addition to the location of the patient at the time of randomization. Categorical variables will be summarized by treatment group using a number (n) and percentage (%). Descriptive statistics such as mean, standard deviation (SD), or median (Q1, Q3) will be calculated for continuous variables.

9.4. EFFICACY ANALYSES

9.4.1. Definition

Time to clinical improvement is defined as :

The time from randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live discharge from the hospital, whichever came first.

9.4.2. ANALYSIS OF THE PRIMARY OUTCOME

The primary endpoint is the median time to clinical improvement by at least 2 points or discharges from the hospital. The number and percent of subjects who met the endpoint by day 14 of follow up will be calculated and tabulated.

The number and percent of subjects who met the endpoint by day 14 of follow up will be calculated and tabulated. The stratified log-rank test will be used to compare median time to clinical improvement between the two treatment arms as the primary analysis. The stratification factor includes clinical site. The hazard ratios and the 95% confidence interval (CI) will be estimated using the Cox model with treatment as the explanatory variable and reported in the table along with number censored and number (%) meeting the endpoint, median time to endpoint, and p-value.

Kaplan-Meier plot of time from randomization to endpoint will be generated (censoring at 14 days if completed follow-up, or at the date of last contact if lost to follow-up prior to 14 days),

A multivariate Cox regression model will also be used to further evaluate the treatment effects on median time to clinical improvement after adjusting for some prognostic factors such as age, race (Arab, non-arab), and other baseline clinical characteristics found significant during univariate analysis.

The proportional hazard assumptions will be examined, and sensitivity analysis may be conducted if appropriate.

9.4.3. ANALYSIS OF SECONDARY ENDPOINT(S)

An adjusted secondary analysis will be conducted using multiple logistic regression analysis for the outcomes such as requirement of ICU admission or mechanical ventilation, 28/ 90 – days mortality will be modeled as the dependent variable and a set of baseline variables that are strongly believed to affect the outcome of Covid-19 will include as independent variables. These independent variables will be included based on found significance during univariate analysis. 28-days and 90-day median survival time will be summarized and

reported using Kaplan–Meier survival curves and will be compared between the study groups using the log-rank test.

QT prolongation is a binary outcome that is assessed repeatedly within participants. This outcome will be analyzed using a generalized estimating equation approach for relative risks with an unstructured variance-covariancematrix(Toeplitz if convergence fails) to accommodate the within-participant correlation. Count outcomes will be analyzed with Poisson regression models. If there is under-or over-dispersion, residuals will be examined to determine the most suitable model (e.g., quasi-Poisson regression, negative binomial regression).

Statistical tests for variables other than the primary outcome will be performed using a two-sided alpha value of 5% to denote significance level. Analysis of secondary outcomes, including safety outcomes, will be compared in the intention-to-treat cohort and will be reported as relative risk with the corresponding 95% CI.

9.5. SAFETY ANALYSIS

9.5.1. ADVERSE EVENTS (AE)

All adverse events will be grouped using Common Terminology Criteria for Adverse Events (CTCAE) V4 of National Institutes of Health (NIH). Adverse events will be grouped into 5 aggregate groups and reported for the entire study period. The groups are: 1) Treatment Emergent Adverse Events (TEAE) 2) Drug related TEAE 3) Grade 3 or higher TEAE 4) Serious Adverse Event 5) On Study Death. All results will be summarized in terms of frequency and percentage and will be compared across study arms using Fisher exact test.

Serious adverse events will be summarized by treatment group using number (n) and percentage (%). The relationship with study treatment will also be summarized. Serious

adverse events related to the study treatment will be summarized by treatment group using a number (n) and percentage (%).

9.5.2. VITAL SIGNS

Vital signs such as Temperature (°C), Respiratory rate, Systolic BP(mmHg), Highest heart rate, oxygen saturation (O2) will be summarized using median (Q1, Q3) at baseline.

9.5.3. LABORATORY PARAMETERS

Laboratory values such as international normalization ratio, platelet count, hemoglobin, white blood cell count, lymphocyte count, glucose, neutrophil count, uric_acid, total bilirubin, AST/SGOT, ALT/SGPT, Blood Urea Nitrogen (BUN), Lactate/Lactic acid, Creatinine, Sodium, Potassium, Procalcitonin, CRP will be summarized at baseline. Figures will be presented for the serial measurements by study visit.

9.5.4. TREATMENT EXPOSURE AND COMPLIANCE

For each group we will report the time of hospital admission to randomization and the time of randomization to the first dose received of the study drugs. We will report the received and duration of study intervention for each group, in addition to the missing or incomplete doses and protocol violations.

9.6. SUBGROUP ANALYSIS

Not Applicable

10. TABLES LISTING AND FIGURES PRESENTATION

Data presentation

- The tests will be presented in the order as in CRF. If not seen in the CRF, will be presented in alphabetical order.
- The TLF tile will be center-aligned and the last row of the title should indicate the population unless specified.
- The column titles should be aligned top left, and the contents in the TLF should be aligned left unless specified.
- TLF will be produced using PROC REPORT in SAS monospace font and pitch 8 in landscape orientation.
- The footnotes will be presented in the order as seen in SAP. No programming notes will be presented in the TLF.

10.1. TABLE SPECIFICATIONS

The following rules will apply when creating the tables.

- Treatment arms will be in columns with the visits in rows unless specified otherwise.
- The values will be aligned on decimal places.
- Number (n) and percentage (%) will be presented in the format n (%).
- Ordering of statistics - <List the order in which the statistics will be presented in the tables>

Number of decimal places (DP)

- For minimum and maximum, the DP's will be the same as the raw data.
- For mean, the DP's will be one more than the raw data.
- For standard deviation (SD) the DP's will be one more than the mean.
- Percentages (%) will be displayed with one DP.

10.2. LISTING SPECIFICATIONS

The following rules will apply when creating the listings.

- Data presented in the listings will be the same as the raw data.
- The values presented in the listing will be left-aligned.
- The listings will be presented by <List the variables in the order they will be presented across all the listings>

Number of decimal places (DP)

- The number of decimal places must be same as in the raw data.

10.3. FIGURES SPECIFICATIONS

The following rules will apply when creating the figures.

- Data presented in the figure will be the same as the raw data.

Number of decimal places (DP)

- Percentages (%) will be displayed with one DP.

11. DATA QUALITY ASSURANCE

Not applicable

12. REPORT GENERATION

12.1. List of Tables Generated

To be included

12.2. LIST OF LISTINGS GENERATED

To be included

12.3. LIST OF FIGURES GENERATED

To be included

13. REFERENCES

1. ICH. ICH harmonised tripartite guideline: statistical principles for clinical trials E9. 1998
2. ASA. Ethical guidelines for statistical practice. Prepared by the Committeeon Professional Ethics.1999. Available from: http://www.amstat.org/about/ethicalguidelines.cfm.
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5. SSAI. The Statistical Society of Australia Inc. Code of Conduct
6. ICH. ICH Harmonised tripartite guideline: guideline for good clinical practice E6. 1996